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SYSTEMATIC REVIEW WITH META-ANALYSIS

REVISIÓN SISTEMÁTICA CON META-ANÁLISIS

REVISÃO SISTEMÁTICA COM METANÁLISE

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Abstract
Systematic reviews with meta-analysis have massive potential for summarizing and evaluating scientific evidence. They address and answer specific complex issues relevant to society, such as those relating to Education and Health. Despite their importance, many studies using this method are conducted with significant methodological weaknesses, such as needing to evaluate the quality of the studies included critically. This text, therefore, represents a support resource for researchers seeking to acquire knowledge about systematic reviews with meta-analysis. To this end, the author of this work discussed the theoretical and methodological elements involved in planning, conducting, and publishing systematic reviews using meta-analysis techniques. He presented examples of studies that adopt appropriate and relevant methodological approaches. Nevertheless, some resources (references to methodological guidelines and digital platforms) have been described to support researchers in the operational path of this type of review. The author hopes this text will elucidate paths and possibilities for advancing scientific research using systematic review with meta-analysis in Brazil and other countries, focused on achieving scientific knowledge with quality and, therefore, social commitment.

Keywords: Systematic reviews; Knowledge synthesis; Methodology; Evidence-based healthcare; Evidence Gaps.

Resumen
Las revisiones sistemáticas con metanálisis tienen un enorme potencial para resumir y evaluar la evidencia científica. Abordan y dan respuesta a cuestiones complejas específicas y relevantes para la sociedad, como las relacionadas con la Educación y la Salud. A pesar de su importancia, muchos estudios que utilizan este método se realizan con importantes debilidades metodológicas, como la necesidad de evaluar críticamente la calidad de los estudios incluidos. Este texto, por tanto, representa un recurso de apoyo para investigadores que buscan adquirir conocimientos sobre revisiones sistemáticas con metanálisis. Para ello,

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el autor de este trabajo discutió los elementos teóricos y metodológicos involucrados en la planificación, realización y publicación de revisiones sistemáticas utilizando técnicas de metanálisis. Presentó ejemplos de estudios que adoptan enfoques metodológicos apropiados y pertinentes. Sin embargo, se han descrito algunos recursos (referencias a guías metodológicas y plataformas digitales) para apoyar a los investigadores en el camino operativo de este tipo de revisión. El autor espera que este texto esclarezca caminos y posibilidades para avanzar en la investigación científica mediante revisión sistemática con metanálisis en Brasil y otros países, enfocados a alcanzar conocimiento científico con calidad y, por tanto, compromiso social.

Palabras clave: Revisiones sistemáticas; Síntesis de conocimientos; Metodología; Atención sanitaria basada en evidencia; Brechas de evidencia.

Resumo

Revisões sistemáticas com metanálise são reconhecidas com grande potencial de sumarizar e avaliar evidências científicas, permitindo abordar e responder determinadas questões complexas e relevantes à sociedade, como aquelas relativas à Educação e Saúde. Apesar da sua importância, muitos estudos com este método são realizados com fragilidades metodológicas importantes, como a não avaliação crítica da qualidade dos estudos incluídos. Portanto, o presente texto representa um recurso de apoio aos pesquisadores que buscam adquirir conhecimentos sobre revisão sistemática com metanálise. Para tanto, buscou-se discutir sobre elementos teóricos e metodológicos que envolvem o planejamento, a condução e a publicação de revisões sistemáticas que utilizam técnicas de metanálise. Exemplos de estudos que adotam condutas metodológicas adequadas e relevantes foram apresentados. Não obstante, alguns recursos (referências de diretrizes metodológicas e plataformas digitais) foram descritas, visando apoiar pesquisadores no percurso operacional deste tipo de revisão. Espera-se que o uso deste texto possa elucidar caminhos e possibilidades para o avanço da pesquisa científica que utiliza a revisão sistemática com metanálise no Brasil e outros países, centrada em realizar o conhecimento científico com qualidade, portanto, com compromisso social.

Palavras-chave: Revisão sistemática; Síntese de conhecimento; Metodologia; Saúde baseada em evidência. Lacunas de Evidências.

Introduction

The realization and dissemination of scientific research has increased dramatically in recent decades with the advance of scientific communication in scientific journals and publishers (Cooper; Hedges; Valentine, 2019; Egger; Higgins; Smith, 2022). Several scientific studies have accompanied this dynamic process, but these works were not necessarily of quality (i.e., theoretical and methodological care so that scientific research answers questions reliably and truthfully) (Egger; Higgins;

Smith, 2022). In particular, some studies approach the same objectives and hypotheses very closely and reach significantly different conclusions (Cooper; Hedges; Valentine, 2019), which has prevented social subjects (researchers, managers, professionals, decision-makers, and the general population) from understanding the events that science seeks to answer and, therefore, make decisions that affect people's lives based on quality scientific evidence (Taylor; Pigott; Williams, 2022; UNICEF, 2023).

Summarizing and evaluating scientific research that addresses specific issues relevant to society, such as Education, Health, and Economics, is crucial so that decisions and practices are based on the best scientific research (Sutton et al., 2019). Advances in scientific methods, techniques, and guidelines that enable knowledge synthesis gained popularity in the 1970s. In particular, since the 1970s, physician, and researcher Archie Cochrane has questioned physicians who did not perform a critical synthesis of relevant clinical studies before adopting a particular clinical practice – a movement that set the standard for the term "systematic review" in the methodological conduct of evidence synthesis (Higgins et al., 2023). In 1976, statistician and researcher Gene Glass complementarily introduced the term "meta-analysis" in his presentation at the *American Educational Research Association* as a statistical technique for summarizing data from similar studies. Although the technique had been used before, his work was the first reference to the term "meta-analysis", a technique used in different fields of knowledge to strengthen the reliability and quality of scientific evidence (Egger; Higgins; Smith, 2022).

Systematic reviews (with and without meta-analysis) have achieved large publication scales in different fields (Karlsson; Takahashi, 2017; UNICEF, 2023). A quick search for review articles on the SciELO electronic portal (https://search.scielo.org/) highlights more than 11,000 review articles published on this portal as of August 15, 2023, with review articles published since 1968 and studies titled "systematic reviews" since 2000, where most apply meta-analysis techniques. More than 300,000 titles can be found in the Virtual Health Library (https://pesquisa.bvsalud.org/)

searching with the word "review" and adopting the "systematic review" filter (with or without meta-analysis), which is equivalent to more than 5,000 studies published every year.

Therefore, the method's growth and recognition must be accompanied by adequate theoretical and methodological implementation to foster evidence-informed health decisions. In particular, some organizations are dedicated to promoting methodological guidelines for the quality of systematic reviews and meta-analyses, such as the *Cochrane Collaboration* (Higgins et al., 2023), the *Joanna Briggs Institute* (JBI, 2020), the *Campbell Collaboration* (Campbell Collaboration, 2021), *and the Evidence Informed Policy Network* (EVIPNet) (Karlsson; Takahashi, 2017). Nevertheless, strengthening the EQUATOR Network *(Enhancing the QUAlity and Transparency Of health Research*) has produced guidelines for drafting scientific research in health, including the specific one for systematic *reviews* with meta-analysis, entitled *The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)*, launched in 2009 and updated in 2020 (Page et al., 2021).

Consequently, this text was written to support researchers who want to perform systematic reviews with meta-analysis with theoretical and methodological quality. To this end, this text highlights the methodological elements involved in planning, running, and publishing systematic reviews with meta-analyses. Nevertheless, examples of studies that adopt recommended methodological approaches and resources (references to methodological guidelines and digital platforms) have been presented to support the reader of this text in the operational path of this type of review.

Methodological framework for Systematic Reviews with Meta-analysis

Table 1 summarizes the methodological elements and resources involved in planning, performing, and publishing systematic reviews with meta-analyses highlighted in this text.

Table 1. Summary of the content and purpose of the sections, and resources for researchers wishing to carry out or begin studies on systematic reviews with meta-analysis.

METHODOLOGICAL BACKGROUND	RECOMMENDATIONS FOR SCIENTIFIC RESEARCH	RESOURCES FOR RESEARCHERS BASED ON THE RECOMMENDATIONS IN THE TEXT	
This section aims to prevent future systematic reviews with meta-analysis from being conducted without considering the fundamental methodological elements, such as a real synthesis of a specific question, a comprehensive search for all relevant studies, and a critical appraisal of the studies.	This section discusses concerns and recommendations for improving scientific research using systematic review and meta-analysis, including reporting resources and good practice examples.	*Multi-tool portal*	• *Campbell Collaboration*: http://systematicreviewtools.com
		Systematic review type (with or without meta-analysis)	• *Right Review*: https://rightreview.knowledgetranslation.net
		Toolkit for assessing the quality/risk of bias of included studies	• *Campbell Collaboration*: http://systematicreviewtools.com/ • *Cochrane Collaboration*: https://training.cochrane.org/handbook/current/chapter-08 • *Critical Appraisal Skills Programme* https://casp-uk.net/casp-tools-checklists/ • *Joanna Briggs Institute*: https://jbi.global/critical-appraisal-tools
		Calculation of individual and combined effect sizes	• Campbell Collaboration: https://www.campbellcollaboration.org/escalc/html/EffectSizeCalculator-SMD5.php • Cochrane Collaboration: https://training.cochrane.org/resource/revman-calculator

Historically, concisely, the systematic review has been understood as a methodological approach to evidence synthesis that allows summarizing, reaching, and critically evaluating scientific evidence on a specific issue (Cooper, Hedges, and Valentine, 2019). However, the proper use of the "systematic review" concept has been improved in recent years. Firstly, due to the design and scope of the different methods and techniques for conducting evidence synthesis that involves scientific research, including the objectives, hypotheses, and methodological characteristics of the different knowledge areas (Munn et al., 2018; Sutton et al., 2019).

For example, Sutton et al. conducted a literature search on the types of reviews performed beyond the systematic review. They mapped 48 different review types, which could be categorized into seven categories. The different conceptualizations and definitions culminated in a broad taxonomy of the different forms of evidence synthesis beyond the classic systematic review, such as the Scoping Review and Rapid Review. Although this text focuses on systematic reviews with meta-analysis, we recommend accessing the *Right Review* portal (see Table 1), which provides definitions, characteristics, and examples of the most different

evidence synthesis types. The portal also includes a taxonomy to help researchers find the most appropriate evidence synthesis method for the research question of interest, including the decision of when to conduct a systematic review with meta-analysis.

The publication of the PRISMA guidelines has stimulated the standardization of the term systematic review (Page et al., 2021). In the current version, labeled PRISMA 2020, the concept of systematic review adopted is that presented in the Cochrane Handbook for systematic reviews (Higgins et al., 2023), which defines a systematic review as "a *review that uses explicit, systematic methods to collate and synthesize findings of studies that address a clearly formulated question*".

An in-depth perspective at the Cochrane Handbook (Higgins et al., 2023) on a systematic review reveals that the authors must collect all the empirical evidence that meets certain eligibility criteria to answer a specific research question, which implies that a systematic review needs to be sufficiently detailed to elucidate the performance of the review, to avoid errors (biases) in scientific research, and to represent a reliable source of conclusions that can ground practical and political decisions on the topic of interest. Operationally, systematic review authors should (Higgins et al., 2023):

- State in detail the specific research question;
- Elucidate, from this research question, the characteristics of the studies eligible to answer the research question;
- Endeavor to find all the relevant studies that answer the question (meet the eligibility criteria) to ensure that conclusions are drawn with minimal selection bias; and
- Critically analyze the included studies to make conclusions and inferences based on all the identified research in an unbiased and objective way (analysis and reporting biases).

Although it seems peculiar to other evidence synthesis methods, the elements of this systematic review description are noteworthy. The first is the specific research question. It differs from other evidence synthesis methods by focusing on a clearly formulated question (based on a specific clinical question).

For example, for systematic reviews on interventions, a clear definition of the population, the intervention, the control/comparison situation, and the outcomes (PICOS mnemonic) must be clarified a priori, which also underpins other stages, such as the selection, description, and critical evaluation of the included studies. We should underscore that the specific questions may be different, such as the diagnosis of some event (for example, tools to diagnose behavioral problems in the classroom) or the association between variables (relationship between school climate and student's academic performance), which is particularly relevant in systematic reviews with meta-analysis, as the validity of the estimates depends on proper and strict methodological conduct. We recommend reading the article by Munn et al., which provides a detailed description of ten different types of systematic review (including meta-analysis), depending on the specific question to be addressed (Munn et al., 2018).

Another critical point to note when conducting a systematic review is a comprehensive and exhaustive literature search strategy that addresses the research question. For example, one study analyzed the methodological conduct of more than 600 biomedical research systematic reviews published up to 2014 (Page et al., 2016). It noted that comprehensive search strategies such as searching unpublished data sources were performed in only 7% of systematic reviews – a significant proportion also adopted restrictive search strategies, such as publication language brackets and searching a few databases. This type of methodological decision generates selection bias in systematic reviews due to the high probability of not including relevant studies, especially those not indexed in the primary databases (Shea et al., 2017), often affecting the discrepancy of inferences in similar systematic reviews. Therefore, the authors of a systematic review with meta-analysis should ensure that they adopt search strategies that cover the scope of the topic to include the

portals that reach the relevant literature on the subject and can be considered in the effect estimates (Cooper; Hedges; Valentine, 2019; JBI, 2020; Egger; Higgins; Smith, 2022; Higgins et al., 2023).

Another relevant methodological characteristic of a systematic review with meta-analysis is the critical appraisal and assessment of the quality of the evidence using appropriate techniques (Cooper, Hedges, and Valentine, 2019). However, an analysis of systematic reviews with and without meta-analysis of biomedical research (Page et al., 2016) observed that the included studies' quality assessment (or risk of bias) was performed in 70% of the reviews. However, only 16% of them used quality assessment to summarize and interpret the results – a critical methodological error. Another analysis of systematic reviews with meta-analyses of educational research found that only 23 out of 56 reviews assessed the studies' quality (Ahn; Ames; Myers, 2012). In a setting with an increasing number of studies with poor methodological conduct, the critical evaluation of studies becomes an essential stage for systematic reviews with meta-analyses, as it allows an objective analysis of the validity of scientific research findings and their conclusions (Shea et al., 2017). Systematic reviews with meta-analysis should employ strategies for critically evaluating studies using available and validated tools for the different types of studies on the topic of interest (see Table 1).

Many systematic review authors seek to answer research questions that include studies where the main result is quantifiable. Therefore, meta-analysis is strongly recommended when it is possible and appropriate to combine the quantitative results of two or more studies. It produces a general statistic and a level of uncertainty that represents an estimate of the study effect, and its variations are available, producing a combined quantitative summary of the results (Higgins et al., 2023). Therefore, meta-analysis is a statistical technique used to synthesize results, preferably from a systematic review, to synthesize all the available evidence on the research question (Schmid, 2021; Egger; Higgins; Smith, 2022).

Conducting a systematic review with meta-analysis has advantages, including increasing the precision of estimates about a research question. In educational research, as in other areas, many interventions are implemented in small schools, classes, or groups of students, and, consequently, studies are too small to provide robust evidence on the results of the intervention in isolation (Ahn; Ames; Myers, 2012; Chernikova et al., 2020; Fishstrom et al., 2022). Another strength of meta-analysis is having procedures to reduce controversies arising from apparently conflicting studies (JBI, 2020; Higgins et al., 2023).

Concurrently, meta-analysis has been conducted inappropriately in a systematic review. Some studies have implemented techniques and procedures incorrectly, jeopardizing the inferences and conclusions of the research, or they sometimes perform meta-analyses when it is inappropriate. In order to clarify these points, some recommendations for scientific research that has conducted a systematic review with meta-analysis are discussed below.

Recommendations for scientific research with Systematic Review with Meta-analysis

Using statistical resources and techniques to synthesize quantitative data does not guarantee that the results are valid in a review any more than it does for a primary study (Cooper, Hedges, and Valentine, 2019). To this end, methodological guidelines for conducting meta-analysis in systematic reviews detail the theoretical elements and procedures required to run a meta-analysis with quality and less probability of systematic errors (Cooper; Hedges; Valentine, 2019; JBI, 2020; Campbell Collaboration, 2021; Schmid, 2021; Egger; Higgins; Smith, 2022; Higgins et al., 2023). Only a few of them are addressed and highlighted here, as they represent initial and vital concerns for authors who aim to know or perform meta-analysis in their scientific research.

Firstly, the clarity and detail of the research question is one of the critical decisions in the systematic review protocol that aims to run a meta-analysis. In particular, it is necessary to detail the research question and understand the methodological approaches of studies suitable for answering it. The studies with methodological designs (experimental, longitudinal, cross-sectional, and even other systematic reviews) may be necessary for the study, depending on the specific question the review intends to answer (Cooper, Hedges, Valentine, 2019; JBI, 2020).

For example, a systematic review with meta-analysis (Vembye; Weiss; Bhat, 2023) aimed to summarize the effects of two teaching models (co-teaching and collaborative) on the academic performance of primary and secondary school students. The authors considered only experimental studies (76 studies in all) to answer this question, as this was the appropriate study design to establish better the relationship between a proposed cause and possible outcomes (Vembye; Weiss; Bhat, 2023) and also allowed for methodological similarity in the design of the studies (i.e., methodological homogeneity), increasing confidence in the inferences and extrapolations of the results of a meta-analysis (Egger; Higgins; Smith, 2022; Higgins et al., 2023; Schmid, 2021).

Another critical point is the conceptual and operational clarity of what is intended as relevant results when drawing up and implementing the protocol. The form of each outcome and its eligible measurement forms should be clearly identified to predict and identify possible statistical and methodological differences in each outcome (Campbell Collaboration, 2021; Higgins et al., 2023; JBI, 2020).

For example, when aiming to perform a systematic review with meta-analysis that includes school performance as an outcome, some studies may have this result as scores, ordinal scales, or categorized aspects (academic success, dichotomized into passing or failing tests or school year). Suppose the study is interested in another crucial educational indicator, such as school attendance. In that case, we should bear that this is another relevant result and, thus, needs to be interpreted separately from other theoretically distinct results (clinical heterogeneity). Breaching this principle is a severe methodological violation and

implies the low validity of the findings of a systematic review with meta-analysis (Cooper, Hedges, and Valentine, 2019). An excellent example of this is a recent systematic review with a meta-analysis on the effect of interventions on academic success and indicators of academic anxiety (two theoretically and clinically distinct indicators) (Fishstrom et al., 2022). Correctly, the authors performed the meta-analysis separately for each relevant outcome.

The proper use of analysis techniques, parameters, and resources is also relevant to improving the quality of systematic reviews through meta-analysis. The principles of meta-analysis involve two stages: summary statistics for each study and summary estimation of the effect of the combined studies (Higgins et al., 2023). In other words, the effect size of the studies individually and combined.

One concern that arises in the first stage is the standardization of effects to be presented and summarized in the protocol. Data types and how to estimate the effect size can vary, even from the same systematic review with meta-analysis. This will imply how outcome data will be compared and presented (JBI, 2020; Page et al., 2021; Higgins et al., 2023).

For example, studies with dichotomous outcomes can use different effect size measures, including odds ratio, relative risk, or a number needed to process. The estimate of the mean difference or a standardized mean difference is usually considered for continuous outcomes (Cooper; Hedges; Valentine, 2019; JBI, 2020; Egger; Higgins; Smith, 2022), relying on formulas to estimate the effect size, such as Cohen's d and Hedge's g (Cooper; Hedges; Valentine, 2019).

The effect size measures should be standardized whenever possible, even if some indicators need to be converted (Shea et al., 2017; Higgins et al., 2023), which allows the results extracted from the studies to be in a consistent or usable format for analysis (Higgins et al., 2023). Nevertheless, it ensures that the interpretation of the direction (benefit or risk and outcome increase or decrease) is made explicit and enables the interpretation of the clinical relevance of the outcome or effect by the authors and readers of the research (Cooper; Hedges; Valentine, 2019; JBI, 2020; Higgins et al., 2023). To this end, Cooper, Hedges, and Valentini (2019) describe

essential procedures for converting effect measures in a meta-analysis and online calculators that allow for converting effect estimates (see Table 1). Another critical point is the authors' search for missing or unreported data in the studies included in a systematic review so that they can be used in meta-analysis procedures (JBI, 2020) or weighted in statistical procedures on analysis biases by studies and missing data (such as imputation) (Higgins et al., 2023).

Models and methods are based on the types of data to be summarized and theoretical and statistical assumptions in the meta-analysis stage of estimating the combined effect size. A primary concern of this stage is assessing whether the variation between the effects of the separate studies is compatible with random variation or large enough to indicate inconsistency between the studies (Schmid, 2021; Egger; Higgins; Smith, 2022), which implies adopting combined effect size estimation models, such as the fixed effects and random effects models (JBI, 2020). These models, combined with statistical methods for estimating the effect (for example, the Mantel-Haenszel method and the inverse variance method) (JBI, 2020), allow for statistical adjustments to estimate the combined effect size and its standard error (which allows us to derive a confidence interval and a P value) (Higgins et al., 2023).

Meta-analysis methods and techniques have advanced to answer complex research questions, for example, meta-analysis of individual patient data, Bayesian, network, multiple, multilevel, and modeling (Cooper; Hedges; Valentine, 2019; Schmid, 2021; Egger; Higgins; Smith, 2022). Using these methods and techniques is necessary to answer the complexity of some research questions and, therefore, must respect certain theoretical and statistical assumptions considered in these methods and techniques. In the field of educational research, a paper (Taylor; Pigott; Williams, 2022) summarizes some of the statistical approaches to meta-analysis in education with complex methods (e.g., meta-analysis of multilevel studies) and resources (calculators) for estimating the combined effect size, which includes the procedures for assessing publication bias, a mandatory stage in a systematic review with meta-analysis (Shea et al., 2017; JBI, 2020; Higgins et al., 2023). The authors of a systematic

review with meta-analysis should involve researchers and statisticians with experience in these assumptions, methods, techniques, and resources (including the statistical packages and software that present these elements) required to run these analyses properly.

A meta-analysis goes beyond estimating an effect or a general association. It explains the statistical differences between studies – that is, the patterns of effect sizes observed (Cooper, Hedges, Valentine, 2019; Egger, Higgins; Smith, 2022). Authors must show concern for a satisfactory explanation and address possible statistical, methodological, and clinical heterogeneity. To this end, they should examine whether the studies' characteristics can explain the results' magnitude or direction (Shea et al., 2017; Page et al., 2021).

For example, a meta-analysis (Chernikova et al., 2020) analyzed the effectiveness of different types of technologies in simulation-based learning environments on complex skills (such as problem-solving and communication) among higher education students. When summarizing the effect of 145 different studies, simulations had a significant and positive overall effect size: Hedge's g = 0.85, 95% confidence interval; 0.69 to 1.02). When performing sub-group and meta-regression analyses, the authors found that the level of initial knowledge and the type of technologies and learning environments were moderators of the effects found – in particular, students with low prior professional knowledge obtained more excellent learning results when supported by examples (practical situations) in the simulations. This allowed the authors to infer that simulations as forms of problem-based learning can be applicable even in the early stages of vocational training courses (in later stages of higher education when students are familiar with the relevant concepts and procedures) (Chernikova et al., 2020).

Finally, progress in conducting systematic reviews with meta-analysis depends on the authors' commitment to detailed reporting faithful to the PRISMA 2020 writing guidelines. One study assessed the impact of the PRISMA 2009 guidelines on the quality of reporting in more than 2,000 systematic reviews after 2009 and observed that the reporting of many items in the PRISMA Statement was

still sub-optimal, especially in the detail of the synthesis of results (including meta-analysis) (Page; Moher, 2017). This fact also led to the PRISMA 2020 version organizing six sub-items on the synthesis of results to ensure, or at least induce, a complete description of the methods adopted to synthesize results, explore possible causes of heterogeneity, and assess the robustness of the synthesized results, including separating the quality of evidence section, which is based on elements estimated in meta-analysis procedures, such as consistency of effect (heterogeneity), imprecision (estimates of the confidence interval of the effect), and publication bias (e.g., funnel plot) (Page et al., 2021; Higgins et al., 2023).

In conclusion, this text highlights the primary concerns and recommendations for researchers who want to conduct or start reading about systematic reviews with meta-analysis. By gathering recommendations and methodological scientific research or examples of reviews with appropriate methodological conduct, the author of this work expects readers to have more elements for planning, conducting, and writing quality reviews of this type. Nevertheless, the resources presented can allow the reader to recognize the steps and processes involved in starting a review. Thus, this author hopes that this text can elucidate paths and possibilities for advancing scientific research that uses systematic review with meta-analysis in Brazil and other countries, focused on achieving scientific knowledge with quality and, therefore, commitment to society.

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